Remarks

Claims 17-21 under 35 U.S.C. 103(a) stand rejected as being unpatentable over Holtzman et al. (US 7,195,761) in view of Seiffert et al. (US 6,518,011). Applicants submit that this rejection is improper for the reasons stated below and respectfully submit that the Examiner has failed to set forth a *prima facie* case of obviousness. As such, Applicants request withdrawal of the rejection.

The Claims are directed to a process for preparing an abeta antibody wherein the method comprises steps of expressing the antibody in cells that endogenously express abeta peptide; adding a beta or gamma secretase inhibitor to media used to grow the cells and purifying the antibody from the growth media wherein the purified antibody has no or low levels of endogenously produced abeta peptide. Some claims are further drawn to the use of mammalian cells including human cells and/or including CHO, HEK 293, PER.C6, and NSO cells.

Applicants respectfully submit that none of the reference alone or in combination teach or suggest **the step of adding secretase inhibitors to media used to grow cells that express abeta antibody as well as endogenously produce Aβ peptide such that the purified antibody has no or low levels of endogenously produced abeta peptide.** The failure of an asserted combination to teach or suggest each and every feature of a claim remains fatal to an obviousness rejection under 35 U.S.C. § 103. Furthermore, neither Holtzman et al. nor Seiffert et al. disclose or-even suggest that the problem of the present invention exists. It therefore follows that the skilled artisan would not be motivated by the cited art to identify the solution provided by the invention. Applicants discuss these points in further detail below.

"All words in a claim must be considered in judging the patentability of that claim against the prior art." MPEP § 2143.03 quoting *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). In order to establish a prima facie case of obviousness, the prior art, including the understanding of one of ordinary skill in the art, must provide a complete teaching of all the claim limitations. See, *eg., In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As the Board of Patent Appeal and Interferences has recently confirmed, a proper obviousness determination requires that the Office "make a searching comparison of the claimed invention - including all its limitations - with the teaching of the prior art." *In re Wada*, Appeal 2007-3733 (BPAI 2008) (quoting *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir.

1995)) (emphasis added by BPAI). "Thus, 'obviousness requires a suggestion of all limitations in a claim."' Id. (quoting *CFMT, Inc. V. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003)).

The Office Action sets a rejection of Claims 17-21 under 35 U.S.C. 103(a) as being unpatentable over Holtzman et al. (US 7,195,761) in view of Seiffert et al. (US 6,518,011). The examiner in the office action acknowledges in her final rejection on October 7, 2009 that while Holtzman teaches a process of expressing an abeta antibody in cells it does not include the step of suppressing abeta peptide production with secretase inhibitor during in vitro cell culture and abeta antibody production. Seifert et al. appears to be cited for the proposition that it teaches the step of suppressing abeta peptide production or accumulation in the presence of gamma sectretase inhibitors in an in vitro cell culture of HEK cells. What the examiner in the office action seems to have overlooked is that Seifert et al. does not express antibodies or teach the suppression of **endogenous** abeta production in HEK cells. Instead Seifert et al. discloses an **assay for suppression of a recombinant epitope tagged beta – APP fragments** in HEK-293 after transfection with HA 11 Beta APP. It does not teach or suggest to a person or ordinary skill in the art to add secretase inhibitors to media used to grow the cells that endogenously express abeta to ensure that the endogenously produced Abeta is suppressed. Moreover, it is unclear whether the compound used to block the over expressed epitope tagged abeta (MDL 28170) is indeed a specific inhibitor of gamma secretase. MDL28170 was identified as an efficient inhibitor of Calpain and CTSL-mediated substrate cleavage and has also been shown to inhibit cathepsin B, as well as other molecules. See Mehdi et al Biochemical and Biophysical Research Communications 1988, 157 (1117-1123); Brana, C., Benham, C. D. & Sundstrom, L. E. 1999 *Eur. J. Neurosci.* **11** (2375-2384); Lubisch et al 2002. Bioorg. Med. Chem Lett. 12 (1335-1338). Therefore, in view of the facts stated above Seifert et al. does not teach a person of ordinary skill in the art the step of suppressing endogenous abeta peptide production in the presence of a gamma secretase inhibitor in an *in vitro* culture.

Even if one were to ignore the significant shortcomings of the cited references, the Office Action nonetheless fails to articulate a reason why one of ordinary skill in the art would combine them. Recent court decisions have stressed that the key to any sustainable rejection under 35 U.S.C. § 103 is the clear articulation of the reasons why the claimed invention would be obvious. Specifically, the Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. § 103 should be made explicit, stating that "rejections

on obviousness cannot be sustained by mere conclusory statements; instead there must be articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR Intl v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (quoting *In re Kahn* 441 F. 3d 977, 988 (Fed. Cir 2006)); see also *Aventis Pharma Deutschland GmbH* v. *Lupin*, Ltd., 499 F.3d 1293, 1301 (Fed. Cir. 2007) (noting that even after KSR, "[ilt remains necessary to show 'some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."')). Moreover, "Office personnel must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art." "Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in KSR Int'l Co. v. Teleflex, Inc." Federal Register Vol. 72 No. 195 at 57528 (October 10, 2007) (emphasis added).

The Office Action summarily concludes (in view of Holtzman et al. and Seifert et al.), "it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to add step of suppressing accumulation or production of abeta peptide of US 6,518,011 to the method of making abeta antibody by cell engineered to express abeta antibody of US 7,195,761 with a reasonable expectation of success in producing abeta peptide pure preparations with no or low content of abeta peptide because it is known to use gamma secretase inhibitors for suppressing abeta peptide production and/or accumulation in an *in vitro* cell culture." Yet, the Office Action contains neither a clear articulation of the teachings or reasons present in the cited art that would motivate one to do that, nor an explicit rationale for the legal conclusion that the claimed invention as a *whole* would have been obvious.

While the cited art may have identified a process of purifying antibodies or possibly the use of non specific gamma secretase inhibitors to inhibit epitope tagged recombinant abeta peptide that is overexpressed in the cell line, neither reference alone or in combination teaches or suggest the suppression of endogenous abeta peptide or elude to the fact that such a suppression of endogenous abeta is indeed important in the purification process of the antibody. Only with the benefit of Applicants' teachings would a person of ordinary skill in the art be motivated to prepare an abeta antibody wherein the method comprises steps of expressing the antibody in cells that endogenously express abeta peptide; adding a beta or gamma secretase inhibitor to media used to grow the cells and purifying the antibody from the growth media such that the purified antibody has no or low

levels of endogenously produced abeta peptide. Applicants submit, therefore, that the rejections of record impermissibly stand on hindsight.

The Office Action seems to minimize Applicants surprising discovery of the problem during the preparation of anti-Aβ antibodies that Aβ peptide (endogenously produced in most mammalian cell lines commonly used to express antibodies) binds to the expressed anti-Aβ antibody at low levels and is carried through the cell culture and purification process. "[A] patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103." *In re Sponnoble*, 405 F.2d 578, 585, 160 USPQ 237, 243 (CCPA 1969).

The Advisory action contends that since the "abeta peptide binds to the anti-abeta antibody and one of skill in the art would be clearly aware of this fact, and thereby recognizes the problem, if the host cell is known to naturally produce abeta peptide." Adding that Holtzman "might be silent about abeta peptide contamination of recombinantly-produced anti-abeta antibody materials because it primary discloses the use of microbial cells or E.coli as particularly useful for making recombinantly-produced anti-abeta antibody materials." Respectfully, Holtzman et al. not only suggests the use of various other mammalian cells (including HEK and CHO cell lines) that naturally produce abeta peptide to express the antibody but also uses a mammalian hybridoma SP2/O cell to express the antibody. Moreover, applicants direct the Examiner to several other disclosures of Abeta production in CHO and NSO cells. See US 2005/0169925 (Bardroff et al.) page 28 paragraph 0171 and US2005/0146512 (Rosenthal et al.) page 21 paragraph 0196. Yet none of these references elude to the problem that the present applicants have identified and are silent as to the existence or possibility of abeta peptide contamination of recombinantly-produced anti-abeta antibody materials. Applicant respectfully submits that the recognition of the problem is gleaned solely from Applicant's specification. MPEP § 2142 states that "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of **the facts gleaned from the prior art**" (emphasis added). "'Any judgment on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and **does not include knowledge**

gleaned only from applicant's disclosure, such a reconstruction is proper'" (MPEP § 2145, quoting *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971), (emphasis added).

CONCLUSION

Applicants respectfully submit that the rejection of claims 17-21 under 35 U.S.C. 103(a) as being unpatentable over Holtzman et al. (US 7,195,761) in view of Seiffert et al. (US 6,518,011 should be reconsidered and withdrawn. For at least the reasons discussed above, Applicants respectfully submit that the claims of the present application are allowable.

If the Examiner has any questions or the Applicant can be of any assistance, the Examiner is invited and encouraged to contact the Applicant's attorney at the number below.
The Commissioner is authorized to charge any necessary fees or credit any overpayment to the Deposit Account No. 05-0840 in the name of Eli Lilly and Company

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